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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,847	10/01/2003	Wouter Bernard Veldhuis	2183-6139US	3770

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EXAMINER	
GALVEZ, JAMES JASON	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,847	VELDHUIS ET AL.	
	Examiner	Art Unit	
	J. Jason Galvez	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/03, 12/03, 2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

Applicant has presented claims 1-17, filed 10/01/2003, that are drawn to a method of treating hypoxia/ischemia related blood flow resistance, including preventing cell death as a result of hypoxia/ischemia. Claims 1-17 are pending. Claims 1-17 are under examination.

Drawings

The drawings are objected to because Fig. 4, 8, and 10 recite "treatbin" of the treatment groups. The heading "treatbin" is either a typographic error or a non-standard heading. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New

Sheet" pursuant to 37 CFR 1.121(d). If the examiner does not accept the changes, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of administering IFN-β to treat hypoxia/ischemia related blood flow resistance, including treating cell death as a result of hypoxia/ischemia, does not reasonably provide enablement for a method of administering functional parts, derivatives, and/or analogues of IFN-β to treat or prevent hypoxia/ischemia related blood flow resistance, including preventing cell death as a result of hypoxia/ischemia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered when determining if the disclosure satisfies the enablement requirement have been summarized as the 1) quantity of experimentation necessary, 2) amount of direction or guidance presented, 3) presence or absence of working examples, 4) nature of the invention, 5) state of the prior art, 6) relative skill of those in the art, 7) predictability or unpredictability of the art, and 8) breath of claims. *Ex*

Parte Forman, (230 USPQ 546 (Bd. Pat. App. & Int. 1986)); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 1-17 are drawn to a method of administering functional parts, derivatives, and/or analogues of IFN-β. Applicant has defined "functional part" to be a part of IFN-β responsible for post-ischemic damage reduction activity. However, what makes up the part of IFN-β responsible for post-ischemic damage reduction activity is not disclosed or known in the art. As such, a person of ordinary skill in the art would not know how to make the invention as claimed. Regarding derivatives and/or analogues of IFN-β, Applicant has not further limited what these molecules may encompass. Therefore, the claims read on any derivative and/or analogue of IFN-β, functional or not, and includes short peptides, as few as 4-5, that may be used to generate antibodies directed to IFN-β. Because the claims read on functions and properties other than the function of interest, a person of ordinary skill in the art would not know how to use the invention as claimed. For example, would a stretch of amino acids used to generate antibodies to IFN-β operate properly in the instant method?

Furthermore, it is well known in the art that protein structure/function activities are highly dependent on primary structure and that alterations in primary structure can affect the activity of the protein of interest. For example, Luck *et al.* have reported that even conservative, single amino acid changes can measurably alter polypeptide activity (Molecular Endocrinology 1991, Vol. 5(12): pp. 1880-1886, esp. p. 1881, table 1). Additionally, nature has demonstrated that even single nucleotide changes can cause altered protein function and phenotypic changes resulting in disease, *e.g.* sickle cell

anemia (Stuart *et al.*, Lancet. 2004, Vol. 364(9442): pp. 1343-1360, esp. p. 1344: column 1, paragraph 2).

Claim 17 is drawn to a method of "at least in part preventing cell death". As such, the claim can be interpreted to mean an absolute prevention of cell death because Applicant merely states "at least". The claim reads on preventing cell death to a single cell, to preventing cell death to every cell. Applicant has shown that IFN-β can decrease lesions following hypoxia/ischemia, but do not show evidence of totally preventing cell death, *i.e.* no lesion. Furthermore, it would not be reasonable to expect a total prevention of cell death following hypoxia/ischemia. There is no evidence in the literature of any treatment that can totally prevent cell death following hypoxia/ischemia, nor has Applicant shown this phenomenon.

For the reasons set forth, without further guidance a person of ordinary skill in the art would not be able to practice the invention commensurate in scope with the claims without undue experimentation.

Claims 1-17 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The factors to be considered when determining if the disclosure satisfies written description requirements include disclosure of complete or partial structure, physical

and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof.

Claims 1-17 are drawn to a method of administering functional parts, derivatives, and/or analogues of IFN-β. The mere recitation a "functional part" defined as part of IFN-β responsible for post-ischemic damage reduction activity is not adequate because the part of IFN-β responsible for post-ischemic damage reduction activity is not disclosed or known in the art. In addition, derivatives and/or analogues of IFN-β were in now way limited by the instant specification. For example ""derivative" can, for instance...", is not limiting (p. 8: [0021]). For the reasons stated, the disclosure does not adequately limit what the functional parts, derivatives, and/or analogues of IFN-β could encompass, which makes the instant method drawn to using a genus of molecules comprising IFN-β.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a partial structure in the form of a functional part, derivative, and/or analogue of IFN-β. There is not even identification of any particular portion of the structure that must be conserved. As stated above, it is not even clear what region of the protein is needed for activity. Accordingly, in the absence of sufficient recitation of distinguishing identifying

characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states: "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, a person of ordinary skill in the art cannot envision the detailed chemical structure of the encompassed genus of polypeptides to be used in the claimed method, and therefore conception is not achieved until reduction to practice has occurred regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention, the compound(s) itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only methods using IFN-β, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is

reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how Applicant plans to identify patients suffering from hypoxia/ischemia related blood flow resistance and how outcomes (*i.e.* treating hypoxia/ischemia related blood flow resistance, improving blood flow, and preventing cell death) are to be measured.

Claims 1-15 are also rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Since there are no recited measurable outcomes, "suitable dose" and "therapeutic dose" is indefinite. What constitutes these doses? Without some measure to establish the effect or outcome, "suitable dose" and "therapeutic dose" are indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wee Yong *et al.* (Neurology 1998, Vol. 51(3): pp. 682-689 **actual pp. 1-15) in view of Boyle *et al.* (Ann Thorac Surg. 1996, Vol. 62(6): pp. 1868-1875) and Saikumar *et al.* (Oncogene 1998, Vol. 17(25): pp. 3341-3349). Wee Yong *et al.* teach IFN-β is immunosuppressive and possesses various anti-inflammatory properties, *e.g.* inhibits T lymphocyte proliferation, reduces production of proinflammatory cytokines, and decreased cell adhesion to endothelial cells (p. 3-5; p. 8: paragraph 1). However, Wee Yong *et al.* do not teach the use of IFN-β to treat hypoxia/ischemia related blood flow resistance, including treating cell death as a result of hypoxia/ischemia.

Boyle *et al.* teach hypoxia/ischemia related blood flow resistance is an inflammatory process and anti-adhesion molecule therapy is effective (p. 1872: Fig. 3; p. 1872: column 2 to p. 1873: column 1, paragraph 1; p. 1873: column 2, paragraph 2). Hypoxia/ischemia related blood flow resistance has been interpreted to encompass a phenomenon termed to "no-reflow" resistance, which is an inability to adequately perfuse previously ischemic tissues. This interpretation has been made in light of the

claim language and the specification where Applicant describes the scenario as "...the microvasculature downstream of the site of obstruction responds by resisting the increased blood flow following removal of the obstruction" (p. 2: [0004]).

Saikumar *et al.* teach the inflammatory process is reponsible for cell death as a result of hypoxia/ischemia (p. 3341: column 2, paragarph 1).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use IFN-β to treat hypoxia/ischemia related blood flow resistance, including treating cell death as a result of hypoxia/ischemia, because hypoxia/ischemia related blood flow resistance, *i.e.* "no-reflow" phenomenon, and cell death is an inflammatory process and IFN-β has anti-inflammatory properties. Additionally, a person of ordinary skill in the art would be motivated to combine the teachings of Wee Yong *et al.*, Boyle *et al.*, and Saikumar *et al.* because hypoxia/ischemia related blood flow resistance, *i.e.* "no-reflow" phenomenon, can occur following successful recanalization and without residual vessel obstruction (Brochet *et al.*, Am Coll Cardiol. 1998, Vol. 32(7): pp. 2011-2017, esp. p. 2011: column 1, paragraph 1). Furthermore, microvasculature integrity, altered during "no-reflow" phenomenon, is essential for myocardial recovery (p. 2011: column 1, paragraph 1). Finally, the expectation of success is reasonably assured because the art teaches IFN-β has anti-inflammatory properties and hypoxia/ischemia related blood flow resistance, including cell death as a result of hypoxia/ischemia, is also known in the art to be an inflammatory process.

It is noted that there is no indication in the art that hypoxia/ischemia is markedly different in various parts of an organism. When blood supply is not adequate to support cellular respiration the cell eventually dies. The brain, heart, limbs, or transplanted organs would all react similarly in response to hypoxia/ischemia. Therefore, IFN-β would be expected to be effective in all recited organs since the consequences of hypoxia/ischemia are the same.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Sano *et al.* (EP 0 797 998 A1; pub. date: 01/1997). Sano *et al.* teach a method of using IFN-β to treat cardiovascular diseases and/or complications (p. 6: lines 1-11). Types of cardiovascular diseases and/or complications include: brain and heart infarction, ischemic vascular disorders, blood flow insufficiency, vascular restenosis, and vascular disorders related to inflammatory processes (column 5: lines 33-59). Furthermore, Sano *et al.* teach the method may be used to treat necrosis as a result of angitis, which leads to "clot formation" and "aneurysm formation" (column 5: lines 51-59). Thus, Sano *et al.* meet the limitations of the claims.

Claims 1-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Sano W. (JP 09151337; pub. date: 10/1997). Sano teaches a method of using IFN-β in the transplantation of organs and to treat various cardiovascular conditions, including restenosis after PTCA, intima hyperplasia after arteriosclerosis, and vasculitis in artery occlusion (see abstract). Furthermore, the method taught by Sano would inherently be effective for reducing cell death following hypoxia/ischemia because, for example, a method directed to treating restenosis following PTCA would inherently, whether appreciated or not, decrease cell death as a result of treating restenosis. Thus, Sano meets the limitations of the claims.

Double Patenting

Claims 1-17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of copending Application No. 10/678,957. Although the conflicting claims are not identical, they are not patentably distinct from each other because both inventions are directed to a method of treating hypoxia/ischemia using interferons. The instant invention is directed to a method of treating hypoxia/ischemia using IFN-β, whereas the copending application is directed to a method of treating hypoxia/ischemia using type I interferons, which is a class of interferons that encompasses IFN-β. The instant application does not specifically recite treating hypoxia/ischemia related inflammation, but this is an inherent consequence of hypoxia/ischemia that is well known in the art (see previously

cited references: Boyle *et al.* and Saikumar *et al.*). The claims correspond, with claims from the instant invention listed, to each other in the following manner:

- Claims 1-14 correspond to claims 1-8 and 15-21 because the claims are both drawn to a method treating hypoxia/ischemia using IFN-β, claimed more generically as IFN type-I in application no. '957.
- Claim 15 corresponds to claim 9 because the claims are both drawn to a method treating hypoxia/ischemia using IFN-β, claimed more generically as IFN type-I in application no. '957, wherein at least one blood vessel is obstructed.
- Claim 16 corresponds to claims 10 and 12-14 because the claims are both drawn to a method of improving blood in post-ischemic tissue using IFN-β, claimed more generically as IFN type-I in application no. '957.
- Claim 17 corresponds to claim 11 because the claims are both drawn to a method of preventing cell death in post-ischemic tissue using IFN-β, claimed more generically as IFN type-I in application no. '957.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

NO CLAIMS ARE ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **J. Jason Galvez, Ph.D**. whose telephone number is

571-272-2935. The examiner can normally be reached Monday through Friday 9 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback, Ph.D.** can be reached at **571-272-0887**.

The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

JANET ANDRES
PRIMARY EXAMINER

JJG
3/28/2005